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Short Communications

Combination of Dacarbazine and Mitomycin in Advanced Colorectal Cancer

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Summary. *Twenty evaluable patients with advanced measurable colorectal cancer received 3-week courses of a combination of IV dacarbazine 300 mg/m²/day from day 1 to day 5 and IV mitomycin 2 mg/m²/day from day 1 to day 5. Fourteen of these patients had had no prior chemotherapy and received two or more courses of this two-drug regimen. None of the patients achieved complete or partial response. Severe to life-threatening myelosuppression, was encountered in patients with prior radiotherapy and or prior chemotherapy, and/or in patients with a Karnofsky score ≤ 70. Hematologic toxicity was mild in the other patients. Nonhematologic toxic effects were generally mild to moderate and consisted essentially in nausea and vomiting. It is concluded that in our hands the regimen selected for this trial has no significant antitumor activity in advanced colorectal cancer.*

Introduction

Advanced colorectal cancer has a dismal prognosis and its treatment remains a major challenge for medical oncologists. Tumor regression may occasionally be achieved with a number of single agents or combination chemotherapy programs. Response rates to these regimens range from 10% to 20% with no major impact on survival.

Encouraging results were recently reported in this disease with a combination of dacarbazine (DTIC, NSC-45388) and mitomycin (MMC, NSC-26980) [2]. Among 26 patients, there were five complete and eight partial responders, with a time to disease progression ranging from 4 to 28 months with a median of 8 months. All patients had received prior therapy with fluorouracil (NSC-19893) alone or in combination with hydroxyurea (NSC-32065) or nitrosourea. These favorable findings prompted us to initiate a confirmatory trial with the same regimen in advanced colorectal cancer.

Materials and Methods

All patients had measurable lesions of histologically proven colorectal carcinoma no longer suitable for surgery or radiation therapy. Measurable tumor was defined as a mass that could be clearly measured by physical examination or on X-rays by a ruler or a caliper. A CAT scan could be used to assess liver and abdominal masses if their largest diameter was at least 5 cm and, whenever possible, if their malignant nature was pathologically demonstrated. Hepatomegaly was accepted as a measurable lesion if malignant invasion was clinically obvious and if the liver edge was clearly defined extending at least 5 cm below the costal margin and/or the xiphoid process during calm respiration. Previously irradiated lesions could not be used for treatment assessment. Eligibility criteria also included an expected survival of at least 2 months, white blood cell count (WBC) ≥ 4,000/mm³, platelets ≥ 100,000/mm³, serum creatinine ≤ 1.5 mg/100 ml, and bilirubin ≤ 2.0 mg/ml. Full recovery from prior therapy was required.

The regimen consisted of DTIC 300 mg/m² as a slow IV infusion under light protection followed by MMC 2 mg/m² as an IV bolus. This treatment was repeated daily for 5 consecutive days and courses were repeated every 3 weeks or upon full recovery from myelosuppression (WBC ≥ 4,000/mm³, platelets > 100,000/mm³). Dose modifications were made according to the hematologic toxicity observed in the previous course. The same modifications were made for each agent. Doses were reduced by 25% with WBC nadir between 1,000 and 2,000/mm³ and/or platelet nadir between 25,000 and 75,000/mm³. Doses were reduced by 50% with lower values and/or significant bleeding secondary to thrombocytopenia.

A minimum of two courses were necessary for treatment assessment unless there was clear disease progression after one course. Response was defined as follows. *Complete response:* absence of all clinically detectable tumor. *Partial response:* reduction by at least 50% of the sum of the products of the two largest perpendicular diameters of the clearly measurable lesions. If hepatomegaly was the primary indicator, a decrease by at least 30% was necessary in the sum of the liver measurements below the costal margin at the midclavicular lines and at the xiphoid process. The reduction in volume of the liver had to be accompanied by a trend to normalization of all pretreatment cholostatic abnormalities in liver function. *Stable disease:* insufficient tumor regression to meet the above criteria of response or < 25% increase in any measurable lesion. *Progression:* increase in a measurable lesion by > 25% and/or appearance of new areas of malignant disease.

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Results

Of 23 eligible patients entered on the trial, three were not evaluable for response evaluation because of treatment withdrawal after one course for toxicity (2) or major protocol violation (1). The 20 evaluable patients comprised nine men and 11 women, with a median age of 62 years (range: 35–71) and a median Karnofsky score of 80 (range: 60–100). The primary tumor originated from the colon in 17 patients and from the rectum in three. Indicator lesions consisted of pulmonary tumor deposits (7), liver metastases (6), abdominal mass (4), lung and liver lesions (2), and nodal sites (1). All but two patients had had prior surgery. Two patients had received prior radiotherapy and three had had prior chemotherapy with chlorozotocin (NSC-178248), sequential fluorouracil and chlorozotocin, or fluorouracil plus lomustine (NSC-79037).

Three patients received one course of therapy, 13 received two courses, two received three courses, and two received four courses. A total of 14 patients who had had no prior chemotherapy received at least two courses of this combination.

None of the patients achieved response to the combination of DTIC and MMC. One patient had stable disease after two courses. The other evaluable patients showed progression after one to four courses. One patient, who ceased to adhere to the protocol because of a severe influenza-like syndrome and was therefore excluded from the analysis of treatment assessment, had marked reduction in serum alkaline phosphatase, γ-glutamyl transpeptidase and CEA levels, and also a disappearance of one out of four liver metastases on CAT scan. This improvement was insufficient to meet the criteria for response, however.

Substantial myelosuppression was encountered in this trial, mainly in patients with prior therapy and/or poor performance status. Of 23 patients, 17 were evaluable for hematologic toxicity. The median WBC ($\times 10^3/mm^3$) was 3.4 (range, 0.1–7.2); it occurred on day 29 (median; range, 20–35) with recovery on day 36 (median; range, 22–44). The median platelet count ($\times 10^3/mm^3$) was 90 (1–231); it occurred on day 22 (median; range, 8–29), with recovery by day 32 (median; range, 15–36). Among the 17 patients evaluable for myelosuppression, seven were fully ambulatory (Karnofsky score $\geq$ 80) and had no prior radio- and/or chemotherapy; the median WBC and platelet nadirs ($\times 10^3/mm^3$) were 4.8 (range, 3.4–7.2) and 120 (range, 85–231), respectively. The corresponding figures for the 10 remaining patients with prior cytotoxic therapy and/or Karnofsky score of $\leq$ 70 were 1.6 (range, 0.1–6.3) and 20 (range, 1–155), respectively; three of these patients had WBC $\leq$ 200 and five had platelets $\leq 28{,}000/mm^3$.

Nonhematological toxic effects in 23 patients consisted essentially in nausea and vomiting, especially on days 1 and 2 of each course (20; severe in 1), stomatitis (2; severe in 1), fever (2; treatment withdrawal for flu-like syndrome in 1), phlebitis (2; extravasation and dermatitis in 1), and severe infection (1). Other toxic manifestations included mild to moderate diarrhea (2), purpura (1), and negligible alopecia (1).

Conclusion

In view of the borderline single-agent activity of MMC [3] and DTIC [4] in advanced colorectal cancer, the report of a 50% response rate in this disease with a combination of these two agents was surprising, particularly in patients who had received prior chemotherapy [2]. None of the 20 evaluable patients included in our trial achieved complete or partial response. Fourteen of these patients had had no prior chemotherapy and received at least two courses of therapy. Nor could any response be found with the same regimen in an interim report on 12 patients with colorectal cancer who had previously been treated with fluorouracil and lomustine in combination [1].

Severe myelosuppression was encountered in our study among patients with prior radiotherapy, prior chemotherapy, and/or performance status of $\leq$ 70 on the Karnofsky scale. Minor hematologic toxicity was seen in the other patients. Nonhematologic toxic effects were mostly mild to moderate and consisted essentially in gastrointestinal intolerance that often resolved after the second day of treatment. It is thus possible that higher dosages might be used in a more favorable patient population, which could result in a higher likelihood of obtaining responses.

The fact that we were unable to reproduce the encouraging findings of Conroy et al. [2] is disappointing and may be ascribed to variations in patient selection, response criteria, or data reporting. These conflicting data provide further evidence of the need for confirmatory trials following successful results in cancer chemotherapy, especially when they are obtained in small series of patients with refractory diseases [5].

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